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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,500	HANAI ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *42-47 and 59-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-41, 48-58 and 63-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/29/2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/29/02; 9/21/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-41, 48-58 and 63-66 in the reply filed on 8/23/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 42-47 and 59-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Drawings

3. The drawings are objected to because Figures 14 and 32 are not labeled as "Fig 14" and "Fig 32", respectively. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s)

should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

4. Claim 63 is objected to as being dependent upon a withdrawn claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 1-41, 48-58 and 63-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-41 and 64-66 are indefinite for reciting "derivative" because the exact meaning of the term is not known. The term "derivative" is not one, which has a universally accepted meaning in the art nor is it one, which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the claimed antibodies are to be derivatized to yield the class of derivatives referred to in

the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "derivative" of the antibody is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "derivative" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, antibody fragments, chemically derivatized molecules, or even antibody mimetics and the specification does not provide a standard for ascertaining the direction, requisite degree or endpoint, one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention. Further, it is unclear what the "derivative" of an antibody actually is. Is the monoclonal antibody or fragment thereof the "derivative of an antibody" or does the monoclonal antibody or fragment thereof serve as a starting point for producing an antibody derivative, i.e., a chimeric or a humanized/human CDR-grafted antibody?

b. Claims 1-41, 48-58 and 63-66 are indefinite for reciting a derivative of a monoclonal antibody which specifically reacts with "ganglioside GD3 which is conjugated..." in claim 1. Is the radioisotope, protein or low molecular weight agent conjugated to GD3 or is the radioisotope, protein or low molecular weight agent conjugated to the antibody derivative?

c. Claim 14 is indefinite for reciting "comprises CDR of an H chain V region and an L chain V region". Does the human CDR-grafted antibody only comprise a single

CDR from an H chain V region and an L chain V region or does the human CDR-grafted antibody comprise all six CDRs from both the H chain and L chain V regions? Which CDR of a heavy chain variable region and a light chain variable region is contemplated by the phrase "comprises CDR of an H chain V region and an L chain V region"?

d. Claims 63-66 recite the limitation "the human CDR-grafted antibody and the antibody fragment thereof". There is insufficient antecedent basis for this limitation in the claim. It is unclear which human CDR-grafted antibody and fragment thereof the phrase refers to. Does the phrase "the human CDR-grafted antibody and the antibody fragment thereof" refer to the human CDR-grafted antibody comprising CDR1, CDR2, CDR3 of the heavy chain V region (i.e., SEQ ID Nos:3-5) or the human CDR-grafted antibody comprising CDR1, CDR2, CDR3 of the light chain V region (i.e., SEQ ID Nos:6-8) or the human CDR-grafted antibody comprising all six CDRs from both the heavy and light chain (i.e., SEQ ID Nos:3-8) or the human CDR grafted antibody comprising the heavy chain V region of SEQ ID NO:9 or the human CDR grafted antibody comprising the light chain V region of SEQ ID NO:54 or the human CDR grafted antibody comprising the heavy chain V region of SEQ ID NO:9 and the light chain V region of SEQ ID NO:54?

e. Claim 7 is indefinite for reciting "the humanized antibody is a human chimeric antibody". As evidenced by Co et al (Nature, 351:501-502, 1991) it is well-established in the art that a chimeric antibody comprises the mouse variable regions joined to human constant regions, whereas a humanized antibody comprises mouse CDRs combined with human frameworks and human constant regions (see Figure 1). Thus, it

is unclear what is meant by the phrase "the humanized antibody is a chimeric antibody" because a humanized antibody and a chimeric antibody are two structurally disparate molecules. Does the phrase "the humanized antibody is a human chimeric antibody" mean that the variable regions of the humanized antibody are chimeric in that they alternate human frameworks and mouse CDRs, for example? Further, it is unclear what the human regions of the "human chimeric antibody" and "human CDR-grafted antibody" are.

f. Claims 7, 48 and 63-66 are indefinite for reciting "human CDR-grafted antibody". While CDR grafting is one method for producing a humanized antibody, it is unclear if the phrase "human CDR-grafted antibody" means that the CDRs are of human origin or not.

g. Claims 1-41, 48-58 and 63-66 are indefinite for reciting "reacts" in claims 1, 48 and 64-66. It is unclear if the term "reacts" means that the antibody catalyzes a chemical reaction such as in the case of catalytic antibodies. Do the claimed antibodies have a catalytic function or do the antibodies just bind the ganglioside GD3?

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 6, 13 and 23 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line, which produces an antibody having the exact chemical identity of antibody KM-641, KM-871 or KM-8871 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is required. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species KM-641, KM-871 and KM-8871.

The specification lacks complete deposit information for the deposit of anti-GD3 antibodies KM-641, KM-871 and KM-8871. It is unclear whether antibodies possessing the identical properties of antibodies KM-641, KM-871 and KM-8871 are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed hybridoma cell line (KM-641) and monoclonal antibodies, this method will not necessarily reproduce hybridoma KM-641 and antibodies, which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive a hybridoma and antibodies identical to those claimed (KM-641, KM-871 and KM-8871). Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed hybridoma KM-641 and antibodies (KM-641, KM-871 and KM-8871).

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed hybridoma KM-641 and antibodies KM-641, KM-871 and KM-8871, a suitable deposit is required for patent purposes, evidence of public availability of the claimed antibody or evidence of the reproducibility without undue experimentation of the claimed antibody, is required.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record

who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of hybridoma KM-641 and cell clones producing antibodies KM-871 and KM-8871 have been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit of hybridoma KM-641 and cell clones producing antibodies KM-871 and KM-8871 are not made under the provisions of the Budapest Treaty, then in order to certify that the deposit complies with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. The specification at page 97 discloses the date of deposit, and the complete name and address of the depository for the cell clone producing antibody KM-8871, however, the specification does not apparently disclose the date of deposit and the complete name and address of the depository for hybridoma KM-641, which produces antibody KM-641 and the cell clone producing KM-871. Alternatively, as an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

The specification provides sufficient guidance and direction for one of ordinary skill in the art to make and/or use human chimeric antibody KM-871 conjugated with human IL-2 (claim 38) and human CDR-grafted antibody KM-8871 conjugated with human IL-2 (claim 40) provided that chimeric antibody KM-871 and CDR-grafted antibody KM-8871 are publicly available (see Examples 2 and 3, beginning at page 97 of the specification). Therefore, a deposit requirement is not made for chimeric antibody KM-871 conjugated with human IL-2 and CDR-grafted antibody KM-8871 conjugated with human IL-2.

9. Claims 24 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibody fragments selected from the group consisting of a Fab, F(ab)2, a single-chain antibody (scFv), a disulfide stabilized antibody fragment (dsFv) wherein said antibody fragments comprise all 6 CDRs, three from the VH domain and three from the VL domain, and wherein said antibody fragments specifically bind or recognize GD3, does not reasonably provide enablement for a peptide comprising CDR that does not contain a full set of 6 CDRs from the VH and the VL domains as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Claim 24 is drawn to a derivative of an antibody comprising a monoclonal antibody or fragment thereof that specifically reacts with GD3 which is conjugated with a radioisotope, a protein or a low molecular weight agent, wherein said antibody fragment is selected from the group consisting of a Fab, F(ab)2, a scFv, a dsFv and a peptide comprising CDR.

The specification discloses only antibody fragments that contain both a VH and a VL and therefore, all six CDRs, three from the heavy chain and three from the light chain and bind ganglioside GD3. The specification does not enable a peptide comprising CDR, which does not contain all 6 CDRs and bind ganglioside GD3.

The claims encompass antibody fragments that only contain a single CDR, which does not contain a full set of 6 CDRs and binds GD3. It is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul,

Fundamental Immunology, (textbook), 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al(Proc. Natl. Acad. Sci. USA 1982 Vol. 79: page 1979). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibody fragments containing only a single CDR as defined by the claim has the required binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of producing antibody fragment containing only a single CDR, resulting in an antibody fragment that specifically binds GD3. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody fragment containing a single CDR as broadly as is claimed.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to antibody fragments containing only a single CDR and specifically bind GD3. Undue experimentation would indeed be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Priority

10. Acknowledgement is made of applicant's claim for foreign priority based on applications filed in Japan, Japan 11/278291, filed 9/30/1999 and Japan 2000-105088, filed 4/6/2000. In view of the intervening art applied below and absent a certified translated copy of Japanese applications, Japan 11/278291 and Japan 2000-105088 as required by 35 U.S.C. 119(b), the instant application is granted the priority date of PCT/JP00/06774, filed 9/29/2000. Upon filing of certified translations of Japan 11/278291 and Japan 2000-105088, which provides adequate written description of the claimed subject matter, the instant application would be granted an effective filing date of 9/30/1999.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-2 and 64-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Chapman et al (Cancer Research, 50:1503-1509, 01 March 1990).

The claims are interpreted as drawn to a derivative of an anti-GD3 monoclonal antibody or fragment thereof, which is conjugated with a radioisotope, a protein or a low molecular weight agent, wherein the anti-GD3 monoclonal antibody is produced by a hybridoma, or is a humanized antibody or is a human antibody. Due to the indefinite nature of the claims the term "derivative" is interpreted to mean that the anti-GD3 antibody is obtained or derived from a hybridoma and also interpreted to mean that the antibody comprises a substituted light chain. For this rejection, the intended use of the claimed anti-GD3 antibody as a medicament, a therapeutic agent for cancers, and as a diagnostic agent for cancers is given no patentable weight. See MPEP 2111.02.

Chapman et al teach monoclonal antibody R24, which is produced by a hybridoma and the antibody binds to the ganglioside GD3 (see page 1503). Chapman et al teach variants of monoclonal antibody R24, in which one (V2-R24) or both light chains (V1-R24) were substituted with MOPC-21 kappa light chain(s), which are interpreted as a derivative of an anti-GD3 monoclonal antibody, R24, produced by a hybridoma (see entire document). Chapman et al teach monoclonal antibody R24 and variants V2-R24 and V1-R24 conjugated to the radioisotope ^{125}I (see page 1504 and Figure 3). Thus, Chapman et al anticipate the claims.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-2, 7-9, 14-16, 24-25, 36-37, 48-51 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapman et al (Cancer Research, 50:1503-

1509, 01 March 1990) in view of Queen et al (U.S. Patent 5,530,101, issued 6/25/1996) and LeBerthon et al (Cancer Research, 51:2694-2698, 1991).

The claims are interpreted as being drawn to a derivative of a monoclonal anti-GD3 antibody produced by a hybridoma, wherein said derivative of a monoclonal antibody is a chimeric or humanized (i.e., human CDR-grafted antibody) anti-GD3 antibody, wherein the chimeric antibody comprises heavy and light chain variable regions of a monoclonal antibody produced by a hybridoma (non-human) and heavy and light chain constant regions of a human antibody and wherein the humanized anti-GD3 antibody comprises heavy and light chain CDRs of a monoclonal antibody against GD3 and human framework regions and constant regions and wherein said anti-GD3 antibody derivative is conjugated with a radioisotope, a protein (i.e., human IL-2 (hIL-2)) or a low molecular weight agent. The claims are also drawn to an antibody fragment comprising the heavy and light chain variable regions of a monoclonal antibody against GD3 produced by a hybridoma, wherein said antibody fragment is selected from a Fab, F(ab)2, scFv, dsFv and a peptide comprising CDR. For this rejection, the intended use of the claimed anti-GD3 antibody as a medicament (claim 64), a therapeutic agent for cancers (claim 65), and as a diagnostic agent for cancers (claim 66) is given no patentable weight. See MPEP 2111.02.

Claim 63 is drafted in the product-by-process format. The recitation of a process limitation in claim 63 is not viewed as positively limiting the claimed product absent a showing that the process of making the human CDR-grafted antibody recited in claim 63 imparts a novel or unexpected property to the claimed product, as it is assumed that

equivalent products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed CDR-grafted antibody and the CDR-grafted antibody of the references. The method in which the CDR-grafted antibody that binds GD3 was produced is immaterial to its patentability. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Chapman et al teach an anti-GD3 monoclonal antibody, R24, produced by a hybridoma (see entire document, particularly page 1503, right column). Chapman et al teach that monoclonal antibody R24 specifically targets the ganglioside GD3 expressed in human melanomas (see entire document, particularly Figures 8-9). Chapman et al teach monoclonal antibody R24 conjugated to the radioisotope ^{125}I (see entire document, particularly Figure 8). Chapman et al do not specifically teach anti-GD3 chimeric and humanized anti-GD3 antibodies or anti-GD3 antibody fragments selected from a Fab, F(ab)2, scFv and dsFv or chimeric and humanized anti-GD3 antibodies conjugated to hIL-2. These deficiencies are made up for in the teachings of Queen et al and LeBerthon et al.

Queen et al teach chimeric and humanized antibodies for human therapy as well as antibody fragments including Fv, Fab, F(ab)2 and single-chain antibodies (scFv) (see entire document, particularly columns 11-16). Queen et al teach that chimeric and

humanized antibodies are less immunogenic in human patients as compared to mouse antibodies (i.e., reduced human anti-mouse antibody (HAMA) response) and thus, overcome one of the limitations associated with mouse antibodies for human therapy (see column 1 and column 16, lines 6-26). Queen et al also teach antibodies conjugated to cytotoxic agents, radionuclides, chemotherapeutic drugs and cytotoxic proteins for treatment of cancerous cells (see column 19, line 45 to column 20, line 22).

LeBerthon et al teach an antibody-hIL-2 immunoconjugate that increases antibody uptake in tumor by a factor of 4 in a time and dose-dependent manner and as stated by LeBerthon et al this opens the door to the development of other immunoconjugates composed of tumor-specific monoclonal antibodies and vasoactive, proinflammatory, or bioregulatory molecules linked by chemical or genetic engineering methods which can alter the microenvironment of tumors (see entire document, particularly Figures 1-6 and page 2698).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a chimeric and humanized R24 anti-GD3 antibody conjugated to hIL-2 for therapeutic benefit of human melanomas.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a chimeric and humanized R24 anti-GD3 antibody conjugated to hIL-2 for therapeutic benefit of human melanomas in view of Chapman et al and Queen et al and LeBerthon et al because Chapman et al teach radioactively labeled monoclonal antibody R24, which specifically targets the ganglioside GD3 expressed in human melanomas and Queen et al teach chimeric and

humanized antibodies for human therapy as well as antibody fragments and chimeric and humanized antibodies are less immunogenic in human patients as compared to mouse antibodies and thus, overcome one of the limitations associated with mouse antibodies for human therapy. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a chimeric and humanized R24 anti-GD3 antibody conjugated to hIL-2 for therapeutic benefit of human melanomas in view of Chapman et al and Queen et al and LeBerthon et al because LeBerthon et al teach an antibody-hIL-2 immunoconjugate that increases antibody uptake in tumor and according to LeBerthon et al this opens the door to the development of other immunoconjugates composed of tumor-specific monoclonal antibodies and vasoactive, proinflammatory, or bioregulatory molecules linked by chemical or genetic engineering methods which can alter the microenvironment of tumors. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Chapman et al and Queen et al and LeBerthon et al and produce a chimeric or humanized R24 antibody or antibody fragment thereof that specifically targets the ganglioside GD3 expressed in human melanomas and it would have been prima facie obvious to conjugate a chimeric and humanized R24 antibody with hIL-2 to specifically increase antibody uptake in tumor for increased therapeutic benefit. Thus, it would have been obvious to one skilled in the art at the time the claimed invention was made to have produced a chimeric and humanized R24 anti-GD3 antibody conjugated to hIL-2 for

therapeutic benefit of human melanomas in view of the teachings of Chapman et al and Queen et al and LeBerthon et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 1-19, 24-29, 33-39, 48-54 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanai et al (Cancer Chemotherapy and Pharmacology, 46 (Suppl):S13-S17, June 2000) as evidenced by Shitara et al [c] (EP 0533199 A2, 3/24/1993) in view of Queen et al (U.S. Patent 5,530,101, issued 6/25/1996) and Nakamura et al (Cancer, 80(12 Suppl):2650-2655, 15 December 1997).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

The claims and their interpretations have been described supra (see item # 14 above).

Claims 3-6 are interpreted as drawn to a derivative of a monoclonal antibody (interpreted as a chimeric or humanized antibody/human CDR grafted antibody) comprising specific CDR VH (SEQ ID Nos:3-5) and/or VL (SEQ ID Nos:6-8) sequences and the monoclonal antibody is produced by hybridoma KM-641 (FERM BP-3116).

Claims 10-13 are interpreted as drawn to a human chimeric antibody (derivative of a monoclonal antibody) that binds GD3 comprising the VH region having the amino acid sequence of SEQ ID NO:55 and/or the VL region having the amino acid sequence

of SEQ ID NO:56 and human chimeric antibody KM-871 having SEQ ID NO:55 (VH) and SEQ ID NO:56 (VL).

Claims 17-19 and 52-54 are interpreted as drawn to a humanized antibody (human CDR-grafted antibody) (derivative of a monoclonal antibody) comprising VH CDRs having the sequences of SEQ ID Nos:3-5, respectively, and/or VL CDRs having the sequences of SEQ ID Nos:6-8, respectively.

Claims 26-29 and 33-35 are interpreted as drawn to an antibody fragment (derivative of a monoclonal antibody) that binds GD3 comprising the VH region having the amino acid sequence of SEQ ID NO:55 and/or the VL region having the amino acid sequence of SEQ ID NO:56 and wherein the antibody fragment comprises VH region CDRs having the sequences of SEQ ID Nos:3-5, respectively, and/or comprises VL region CDRs having the sequences of SEQ ID Nos:6-8.

Claims 38 and 39 are drawn to chimeric antibody KM-871 conjugated with human IL-2 (hIL-2), wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:57 (i.e., heavy chain variable region of KM-871 (KM-641) fused to hIL-2) and the light chain variable region comprises the amino acid sequence of SEQ ID NO:56.

Hanai et al teach chimeric antibody KM-871 that specifically reacts with GD3 and KM-871 comprises the constant region of human IgG1 linked to the variable regions of the mouse monoclonal antibody KM-641, which is produced by hybridoma KM-641 (FERM BP-3116) as evidenced by Shitara et al [c] (see page 7, lines 10-12). Further, as evidenced by Shitara et al [c] monoclonal antibody KM-641 comprises a VH chain

having the amino acid sequence of SEQ ID NO:55 (identical to SEQ ID NO:4 of Shitara et al [c], see page 29) and a VL chain having the amino acid sequence of SEQ ID NO:56 (identical to SEQ ID NO:5 of Shitara et al [c], see page 30), and the VH chain of SEQ ID NO:55 comprises CDR1, CDR2 and CDR3 having the sequences of SEQ ID Nos:3, 4 and 5, respectively, and the VL chain of SEQ ID NO:56 comprises CDR1, CDR2 and CDR3 having the sequences of SEQ ID Nos:6, 7 and 8, respectively. Thus, the chimeric antibody taught by Hanai et al, which comprises the VH and VL chains from mouse monoclonal antibody KM-641 (SEQ ID Nos:4 and 5 at pages 29-30 of Shitara et al) necessarily comprises the claimed VH and VL sequences (SEQ ID Nos:55 and 56), which, in turn, necessarily comprises the claimed CDR sequences (SEQ ID Nos:3-8). Hanai et al do not specifically teach chimeric antibody KM-871 conjugated with a radioisotope, a protein or a low molecular weight agent, or a humanized/human CDR-grafted antibody comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or an antibody fragment comprising the VH chain of SEQ ID NO:55 and/or the VL chain of SEQ ID NO:56 or comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or wherein the antibody derivative (chimeric, humanized and antibody fragment) is conjugated to human IL-2. These deficiencies are made up for in the teachings of Queen et al and Nakamura et al.

Queen et al have been described supra.

Nakamura et al teach an I^{125} labeled antibody-human IL-2 (hIL-2) immunoconjugate that specifically enhances tumor vascular permeability whereas

pretreatment with IL-2 was not tumor specific (see page 2651, left column, Figure 2 and page 2655).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Hanai et al as evidenced by Shitara et al [c] and Queen et al and Nakamura et al because Hanai et al teach chimeric antibody KM-871 that specifically reacts with GD3 expressed in human tumors and KM-871 comprises the constant region of human IgG1 linked to the variable region of the mouse monoclonal antibody KM-641, which is produced by hybridoma KM64 (FERM BP-3116) as evidenced by Shitara et al. Thus, KM-871 necessarily comprises the KM-641 VH and VL chains of SEQ ID Nos:55 and

56, respectively, and necessarily comprises VH CDRs of SEQ ID Nos:3-5 and VL CDRs of SEQ ID Nos:6-8 and Nakamura et al teach an I^{125} labeled antibody-hIL-2 immunoconjugate specifically enhances tumor vascular permeability whereas pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conjugated hIL-2 to chimeric antibody KM-871 taught by Hanai et al to specifically increase tumor vascular permeability, thereby enhancing therapeutic efficacy of chimeric antibody KM-871 in human tumors. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to human IL-2 for therapeutic benefit of human tumors in view of Hanai et al as evidenced by Shitara et al [c] and Queen et al and Nakamura et al because Hanai et al teach an anti-GD3 antibody (KM-871) comprising VH CDRs of SEQ ID Nos:3-5 and VL CDRs of SEQ ID Nos:6-8 and Queen et al teach humanized antibodies for human therapy as well as antibody fragments and humanized antibodies are less immunogenic in human patients (i.e., reduced HAMA response) as compared to mouse antibodies, thereby overcoming one of the limitations associated with mouse antibodies for human therapy and Nakamura et al teach an I^{125} labeled antibody-hIL-2 immunoconjugate specifically enhances tumor vascular permeability

whereas pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have produced a GD3 specific humanized antibody and antibody fragments thereof comprising VH CDRs of SEQ ID Nos:3-5 and/or VL CDRs of SEQ ID Nos:6-8 (CDRs of KM-871) as taught by Hanai et al as evidenced by Shitara et al [c] and anti-GD3 antibody fragments comprising the VH and VL chains of SEQ ID Nos:55 and 56 (i.e., VH and VL chains of KM-871), respectively, and one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to conjugate hIL-2 to the anti-GD3 humanized antibody and antibody fragments thereof in order to specifically enhance tumor vascular permeability of the antibodies for increased therapeutic benefit of human tumors. Thus, it would have been obvious to one skilled in the art at the time the claimed invention was made to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to human IL-2 for therapeutic benefit of human tumors in view of Hanai et al as evidenced by Shitara et al [c] and Queen et al and Nakamura et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

16. Claims 1-19, 24-29, 33-39, 48-54 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shitara et al [a] (U.S. Patent 5,750,078, issued 5/12/1998) in view of Queen et al (U.S. Patent 5,530,101, issued 6/25/1996) and Nakamura et al (Cancer, 80(12 Suppl):2650-2655, 15 December 1997).

The claims and their interpretations have been described supra (see item nos. 14 and 15 above).

Shitara et al [a] teach chimeric antibody KM-871 that specifically reacts with GD3 (see Table 1 at column 30), which is expressed in human tumors (i.e., melanoma) and KM-871 comprises the constant region of human IgG1 linked to the variable regions of the mouse monoclonal antibody KM-641, which is produced by hybridoma KM-641 (FERM BP-3116) (see columns 8-10). Thus, chimeric antibody KM-871 taught by Shitara et al [a] comprises the VH and VL chains from mouse monoclonal antibody KM-641 (SEQ ID Nos:4 and 5, see columns 37-40), which in turn, comprise the claimed VH CDR sequences (SEQ ID Nos:3-5, see residues 31-35, 50-66 and 99-108 of SEQ ID NO:4 at columns 37-38) and VL CDR sequences (SEQ ID Nos:6-8, see residues 24-34, 50-56 and 89-97 of SEQ ID NO:5 at columns 39-40). Shitara et al [a] do not specifically teach chimeric antibody KM-871 conjugated with a radioisotope, a protein (i.e., IL-2) or a low molecular weight agent, or a humanized/human CDR-grafted antibody comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or an antibody fragment comprising the VH chain of SEQ ID NO:55 and/or the VL chain of SEQ ID NO:56 or comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or wherein the antibody derivative (chimeric, humanized

and antibody fragment) is conjugated to human IL-2 (hIL-2). These deficiencies are made up for in the teachings of Queen et al and Nakamura et al

Queen et al have been described supra.

Nakamura et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [a] and Queen et al and Nakamura et al because Shitara et al [a] teach chimeric antibody KM-871 that specifically reacts with GD3 expressed in human tumors and KM-871 comprises the constant region of human IgG1 linked to the variable region of the mouse monoclonal antibody KM-641, which is produced by hybridoma

KM64 (FERM BP-3116). Thus, KM-871 comprises the KM-641 VH and VL chains of SEQ ID Nos:55 and 56, respectively, and comprises VH CDRs of SEQ ID Nos:3-5 and VL CDRs of SEQ ID Nos:6-8 and Nakamura et al teach an I^{125} labeled antibody-hIL-2 immunoconjugate specifically enhances tumor vascular permeability whereas pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conjugated hIL-2 to chimeric antibody KM-871 taught by Shitara et al [a] to specifically enhance tumor vascular permeability, thereby enhancing the therapeutic efficacy of chimeric antibody KM-871 in human tumors. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [a] and Queen et al and Nakamura et al because Shitara et al [a] teach an anti-GD3 antibody (KM-871) comprising VH CDRs of SEQ ID Nos:3-5 and VL CDRs of SEQ ID Nos:6-8 and administered mouse monoclonal antibodies illicit an anti-mouse antibody response in human patients (see column 2, lines 18-23) and Queen et al teach humanized antibodies for human therapy, which are less immunogenic in human patients as compared to mouse antibodies (i.e., reduced HAMA response) and thus, overcome one of the limitations associated with administering

mouse antibodies for human therapy and Nakamura et al teach an I^{125} labeled antibody-hIL-2 immunoconjugate specifically enhances tumor vascular permeability whereas pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have produced a GD3 specific humanized antibody and antibody fragments thereof comprising VH CDRs of SEQ ID Nos:3-5 and/or VL CDRs of SEQ ID Nos:6-8 as taught by Shitara et al [a] and anti-GD3 antibody fragments comprising the VH and VL chains of SEQ ID Nos:55 and 56 (i.e., VH and VL chains of KM-871), respectively, and one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to conjugate hIL-2 to the anti-GD3 humanized antibody and antibody fragments to specifically enhance tumor vascular permeability of the antibodies for increased therapeutic benefit of human tumors. Thus, it would have been obvious to one skilled in the art at the time the claimed invention was made to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [a] and Queen et al and Nakamura et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

17. Claims 1-19, 24-29, 33-39, 48-54 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shitara et al [b] (U.S. Patent 6,437,098 B1, priority to 9/17/1992) in view of Queen et al (U.S. Patent 5,530,101, issued 6/25/1996) and Nakamura et al (Cancer, 80(12 Suppl):2650-2655, 15 December 1997).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The claims and their interpretations have been described supra (see item nos. 14 and 15 above).

Shitara et al [b] teach chimeric antibody KM-871 that specifically reacts with GD3 (see Table 1 at column 30), which is expressed in human tumors (i.e., melanoma) and KM-871 comprises the constant region of human IgG1 linked to the variable regions of the mouse monoclonal antibody KM-641, which is produced by hybridoma KM-641 (FERM BP-3116) (see columns 8-10). Thus, chimeric antibody KM-871 taught by Shitara et al [b] comprises the VH and VL chains from mouse monoclonal antibody KM-641 (SEQ ID Nos:18 and 19, see columns 45-48), which in turn, comprise the claimed VH CDR sequences (SEQ ID Nos:3-5, see residues 31-35, 50-66 and 99-108 of SEQ ID NO:18 at columns 45-46) and VL CDR sequences (SEQ ID Nos:6-8, see residues 24-34, 50-56 and 89-97 of SEQ ID NO:19 at columns 47-48). Shitara et al [b] do not specifically teach chimeric antibody KM-871 conjugated with a radioisotope, a protein (i.e., IL-2) or a low molecular weight agent, or a humanized/human CDR-grafted antibody comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or an antibody fragment comprising the VH chain of SEQ ID NO:55 and/or the VL chain of SEQ ID NO:56 or comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or wherein the antibody derivative (chimeric, humanized and antibody fragment) is conjugated to human IL-2 (hIL-2). These deficiencies are made up for in the teachings of Queen et al and Nakamura et al

Queen et al have been described supra.

Nakamura et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [b] and Queen et al and Nakamura et al because Shitara et al [b] teach chimeric antibody KM-871 that specifically reacts with GD3 expressed in human tumors and KM-871 comprises the constant region of human IgG1 linked to the variable region of the mouse monoclonal antibody KM-641, which is produced by hybridoma KM64 (FERM BP-3116). Thus, KM-871 comprises the KM-641 VH and VL chains of SEQ ID Nos:55 and 56, respectively, and comprises VH CDRs of SEQ ID Nos:3-5 and VL CDRs of SEQ ID Nos:6-8 and Nakamura et al teach an I^{125} labeled antibody-hIL-2 immunoconjugate specifically enhances tumor vascular permeability whereas

pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conjugated hIL-2 to chimeric antibody KM-871 taught by Shitara et al [b] to specifically increase tumor vascular permeability, thereby enhancing the therapeutic efficacy of chimeric antibody KM-871 in human tumors. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [b] and Queen et al and Nakamura et al because Shitara et al [b] teach an anti-GD3 antibody (KM-871) comprising VH CDRs of SEQ ID Nos:3-5 and VL CDRs of SEQ ID Nos:6-8 and administered mouse monoclonal antibodies illicit an anti-mouse antibody response in human patients (see column 2, lines 18-23) and Queen et al teach humanized antibodies for human therapy, which are less immunogenic in human patients as compared to mouse antibodies (i.e., reduced HAMA response) and thus, overcome one of the limitations associated with administering mouse antibodies for human therapy and Nakamura et al teach an I^{125} labeled antibody-hIL-2 immunoconjugate specifically enhances tumor vascular permeability whereas pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have produced a

GD3 specific humanized antibody and antibody fragments thereof comprising VH CDRs of SEQ ID Nos:3-5 and/or VL CDRs of SEQ ID Nos:6-8 as taught by Shitara et al [a] and anti-GD3 antibody fragments comprising the VH and VL chains of SEQ ID Nos:55 and 56 (i.e., VH and VL chains of KM-871), respectively, and one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to conjugate hIL-2 to the anti-GD3 humanized antibody and antibody fragments thereof to specifically enhance tumor vascular permeability of the antibodies for increased therapeutic benefit of human tumors. Thus, it would have been obvious to one skilled in the art at the time the claimed invention was made to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [b] and Queen et al and Nakamura et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

18. Claims 1-19, 24-29, 33-39, 48-54 and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shitara et al [c] (EP 0533199 A2, published 3/24/1993) in view of Queen et al (U.S. Patent 5,530,101, issued 6/25/1996) and Nakamura et al (Cancer, 80(12 Suppl):2650-2655, 15 December 1997).

The claims and their interpretations have been described supra (see item nos. 14 and 15 above).

Shitara et al [c] teach chimeric antibody KM-871 that specifically reacts with GD3 (see Table 1 at page 22), which is expressed in human tumors (i.e., melanoma) and KM-871 comprises the constant region of human IgG1 linked to the variable regions of the mouse monoclonal antibody KM-641, which is produced by hybridoma KM-641 (FERM BP-3116) (see pages 7-8 and Example 2 at page 18). Thus, chimeric antibody KM-871 taught by Shitara et al [c] comprises the VH and VL chains from mouse monoclonal antibody KM-641 (SEQ ID Nos:4 and 5, see pages 29-30), which in turn, comprise the claimed VH CDR sequences (SEQ ID Nos:3-5, see residues 31-35, 50-66 and 99-108 of SEQ ID NO:4 at page 29) and VL CDR sequences (SEQ ID Nos:6-8, see residues 24-34, 50-56 and 89-97 of SEQ ID NO:5 at page 30). Shitara et al [c] do not specifically teach chimeric antibody KM-871 conjugated with a radioisotope, a protein (i.e., hIL-2) or a low molecular weight agent, or a humanized/human CDR-grafted antibody comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or an antibody fragment comprising the VH chain of SEQ ID NO:55 and/or the VL chain of SEQ ID NO:56 or comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or wherein the antibody derivative (chimeric, humanized and antibody fragment) is conjugated to human IL-2 (hIL-2). These deficiencies are made up for in the teachings of Queen et al and Nakamura et al.

Queen et al have been described supra.

Nakamura et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [c] and Queen et al and Nakamura et al because Shitara et al [c] teach chimeric antibody KM-871 that specifically reacts with GD3 expressed in human tumors and KM-871 comprises the constant region of human IgG1 linked to the variable region of the mouse monoclonal antibody KM-641, which is produced by hybridoma KM64 (FERM BP-3116). Thus, KM-871 comprises the KM-641 VH and VL chains of SEQ ID Nos:55 and 56, respectively, and comprises VH CDRs of SEQ ID Nos:3-5 and VL CDRs of SEQ ID Nos:6-8 and Nakamura et al teach an I^{125} labeled antibody-hIL-2

immunoconjugate specifically enhances tumor vascular permeability whereas pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conjugated hIL-2 to chimeric antibody KM-871 taught by Shitara et al [c] to specifically enhance tumor vascular permeability, thereby enhancing the therapeutic efficacy of chimeric antibody KM-871 in human tumors. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [c] and Queen et al and Nakamura et al because Shitara et al [c] teach an anti-GD3 antibody (KM-871) comprising VH CDRs of SEQ ID Nos:3-5 and VL CDRs of SEQ ID Nos:6-8 and administered mouse monoclonal antibodies illicit an anti-mouse antibody response in human patients (see column 2, lines 18-23) and Queen et al teach humanized antibodies for human therapy, which are less immunogenic in human patients as compared to mouse antibodies (i.e., reduced HAMA response) and thus, overcome one of the limitations associated with administering mouse antibodies for human therapy and Nakamura et al teach an I^{125} labeled antibody-hIL-2 immunoconjugate specifically enhances tumor vascular permeability whereas pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to

one of ordinary skill in the art at the time the invention was made to have produced a GD3 specific humanized antibody and antibody fragments thereof comprising VH CDRs of SEQ ID Nos:3-5 and/or VL CDRs of SEQ ID Nos:6-8 as taught by Shitara et al [c] and anti-GD3 antibody fragments comprising the VH and VL chains of SEQ ID Nos:55 and 56 (i.e., VH and VL chains of KM-871), respectively, and one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to conjugate hIL-2 to the anti-GD3 humanized antibody and antibody fragments thereof to specifically enhance tumor vascular permeability of the antibodies for increased therapeutic benefit of human tumors. Thus, it would have been obvious to one skilled in the art at the time the claimed invention was made to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [c] and Queen et al and Nakamura et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 1-19, 24-29, 33-39, 48-54 and 63-66 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim claims 1-4 of U.S. Patent No. 6,437,098 B1 in view of Queen et al ((U.S. Patent 5,530,101, issued 6/25/1996) and Nakamura et al (Cancer, 80(12 Suppl):2650-2655, 15 December 1997).

The claims and their interpretations have been described supra (see item nos. 14 and 15 above).

Claims 1-4 of U.S. Patent 6,437,098 B1 are drawn to a chimeric antibody comprising heavy and light chain variable regions of mouse monoclonal antibody Km-641 produced by transformant KM-641 (FERM BP-3116) and the heavy and light chain constant regions of a human antibody, wherein said chimeric antibody binds ganglioside GD3 and wherein the chimeric antibody comprises a heavy chain variable region that has the amino acid sequence of residues 11 to 129 of SEQ ID NO:18 and/or comprises a light chain variable region that has the amino acid sequence of residues 21-127 of SEQ IOD NO:19. The sequences of residues 11-129 of SEQ ID NO:18 and residues 21-127 of SEQ ID NO:19 are identical to the sequences of instantly claimed SEQ ID

Nos:55 and 56 (i.e., variable regions of KM-641) and also comprise VH CDRs of SEQ ID Nos:3-5 and VL CDRs of SEQ ID Nos:6-8 and thus, anticipate the instant claims drawn to a derivative of an antibody (interpreted as a chimeric antibody) and a human chimeric antibody comprising VH CDRs of SEQ ID Nos:3-5 and/or VL CDRs of SEQ ID Nos:6-8 and comprising the VH sequence of SEQ ID NO:55 and/or the VL sequence of SEQ ID NO:56. The claims in U.S. Patent 6,437,098 B1 do not specifically teach an anti-GD3 chimeric antibody conjugated with a radioisotope, a protein (i.e., hIL-2) or a low molecular weight agent, or a humanized/human CDR-grafted antibody comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or an antibody fragment comprising the VH chain of SEQ ID NO:55 and/or the VL chain of SEQ ID NO:56 or comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or wherein the antibody derivative (chimeric, humanized and antibody fragment) is conjugated to hIL-2. These deficiencies are made up for in the teachings of Queen et al and Nakamura et al.

Queen et al have been described supra.

Nakamura et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have conjugated an anti-GD3 chimeric antibody to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s)

produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have conjugated an anti-GD3 chimeric antibody to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Queen et al and Nakamura et al because Nakamura et al teach an I^{125} labeled antibody-hIL-2 immunoconjugate specifically enhances tumor vascular permeability whereas pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conjugated hIL-2 to the anti-GD3 chimeric antibody of U.S. Patent 6,437,098 B1 to specifically enhance tumor vascular permeability, thereby enhancing the therapeutic efficacy of the chimeric antibody in human tumors. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have conjugated an anti-GD3 chimeric antibody to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized

antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Queen et al and Nakamura et al because Queen et al teach humanized antibodies for human therapy, which are less immunogenic in human patients as compared to mouse antibodies and even chimeric antibodies (i.e., reduced HAMA response) and thus, overcome one of the limitations associated with administering mouse or chimeric antibodies for human therapy and Nakamura et al teach an I^{125} labeled antibody-hIL-2 immunoconjugate specifically enhances tumor vascular permeability whereas pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have produced a GD3 specific humanized antibody and antibody fragments thereof comprising VH CDRs of SEQ ID Nos:3-5 and/or VL CDRs of SEQ ID Nos:6-8 and anti-GD3 antibody fragments comprising the VH and VL chains of SEQ ID Nos:55 and 56, respectively, and one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to conjugate hIL-2 to the anti-GD3 humanized antibody and antibody fragments thereof to specifically enhance tumor vascular permeability of the antibodies for increased therapeutic benefit of human tumors. Thus, it would have been obvious to one skilled in the art at the time the claimed invention was made to have conjugated an anti-GD3 chimeric antibody to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody

fragments to hIL-2 for therapeutic benefit of human tumors in view of Queen et al and Nakamura et al.

Claims 1-19, 24-29, 33-39, 48-54 and 63-66 are directed to an invention not patentably distinct from claims 1-4 of commonly assigned U.S. Patent 6,437,098 B1. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned U.S. Patent 6,437,098 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

21. Claims 1-19, 24-29, 33-39, 48-54 and 63-66 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim claims 1-2 of U.S. Patent No. 5,750,078 in view of Shitara et al [c] (EP 0533199 A2,

published 3/24/1993) and Queen et al ((U.S. Patent 5,530,101, issued 6/25/1996) and Nakamura et al (Cancer, 80(12 Suppl):2650-2655, 15 December 1997).

The claims and their interpretations have been described supra (see item nos. 14 and 15 above).

Claims 1-2 of U.S. patent 5,750,078 are drawn to a pharmaceutical composition comprising a human chimeric antibody KM-871 produced by a transformant KM-871 (FERM BP-3512, which is reactive with ganglioside GD3 and a human chimeric antibody KM-871 produced by a transformant KM-871 (FERM BP-3512, which is reactive with ganglioside GD3. Claims 1-2 of U.S. Patent 5,750,078 do not specifically teach the variable region sequences of chimeric antibody KM-871 or chimeric antibody KM-871 conjugated with a radioisotope, a protein (i.e., hIL-2) or a low molecular weight agent, or a humanized/human CDR-grafted antibody comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or an antibody fragment comprising the VH chain of SEQ ID NO:55 and/or the VL chain of SEQ ID NO:56 or comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or wherein the antibody derivative (chimeric, humanized and antibody fragment) is conjugated to human IL-2 (hIL-2). These deficiencies are made up for in the teachings of Shitara et al [c] and Queen et al and Nakamura et al.

Shitara et al [c] have been described supra.

Queen et al have been described supra.

Nakamura et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [c] and Queen et al and Nakamura et al because Shitara et al [c] teach chimeric antibody KM-871 (produced by transformant KM-871 (FERM BP-3512); see page 7, lines 46-50) that specifically reacts with GD3 expressed in human tumors and KM-871 comprises the constant region of human IgG1 linked to the variable region of the mouse monoclonal antibody KM-641, which is produced by hybridoma KM-641 (FERM BP-3116). Thus, KM-871 comprises the KM-641 VH and VL chains of SEQ ID Nos:55 and 56, respectively, and comprises VH CDRs of SEQ ID Nos:3-5 and VL CDRs of SEQ ID Nos:6-8 and Nakamura et al teach an I^{125} labeled antibody-hIL-2

immunoconjugate specifically enhances tumor vascular permeability whereas pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conjugated hIL-2 to chimeric antibody KM-871 taught by Shitara et al [c] to specifically increase tumor vascular permeability, thereby enhancing the therapeutic efficacy of chimeric antibody KM-871 in human tumors. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [c] and Queen et al and Nakamura et al because Shitara et al [c] teach an anti-GD3 antibody (KM-871) comprising VH CDRs of SEQ ID Nos:3-5 and VL CDRs of SEQ ID Nos:6-8 and administered mouse monoclonal antibodies illicit an anti-mouse antibody response in human patients (see column 2, lines 18-23) and Queen et al teach humanized antibodies for human therapy, which are less immunogenic in human patients as compared to mouse antibodies (i.e., reduced HAMA response) and thus, overcome one of the limitations associated with administering mouse antibodies for human therapy and Nakamura et al teach an I^{125} labeled antibody-hIL-2 immunoconjugate specifically enhances tumor vascular permeability whereas pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to

one of ordinary skill in the art at the time the invention was made to have produced a GD3 specific humanized antibody and antibody fragments thereof comprising VH CDRs of SEQ ID Nos:3-5 and/or VL CDRs of SEQ ID Nos:6-8 as taught by Shitara et al [c] and anti-GD3 antibody fragments comprising the VH and VL chains of SEQ ID Nos:55 and 56 (i.e., VH and VL chains of KM-871), respectively, and one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to conjugate hIL-2 to the anti-GD3 humanized antibody and antibody fragments thereof to specifically enhance tumor vascular permeability of the antibodies for increased therapeutic benefit of human tumors. Thus, it would have been obvious to one skilled in the art at the time the claimed invention was made to have conjugated chimeric antibody KM-871 to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [c] and Queen et al and Nakamura et al.

Claims 1-19, 24-29, 33-39, 48-54 and 63-66 are directed to an invention not patentably distinct from claims 1-2 of commonly assigned U.S. Patent 5,750,078. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned U.S. Patent 5,750,078, discussed above, would form the

basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

22. Claims 1-19, 24-29, 33-39, 48-54 and 63-66 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim claims 1-2 of U.S. Patent No. 6,495,666 B2 in view of Shitara et al [c] (EP 0533199 A2, published 3/24/1993) and Queen et al ((U.S. Patent 5,530,101, issued 6/25/1996) and Nakamura et al (Cancer, 80(12 Suppl):2650-2655, 15 December 1997).

The claims and their interpretations have been described supra (see item nos. 14 and 15 above).

Claims 1-2 of U.S. patent 6,495,666 B2 are drawn to a polypeptide comprising the amino acid sequence of residues 11 to 129 of SEQ ID NO:18 and a polypeptide comprising the amino acid sequence of residues 21-127 of SEQ ID NO:19, which as

evidenced by the disclosure of U.S. Patent 6,495,666 B2 these polypeptides are the VH and VL regions of KM-641, which is a monoclonal antibody that binds GD3. Claims 1-2 of U.S. Patent 6,495,666 B2 do not specifically teach a anti-GD3 chimeric antibody comprising the VH and VL regions of KM-641 (i.e., chimeric antibody KM-871) conjugated with a radioisotope, a protein (i.e., hIL-2) or a low molecular weight agent, or a humanized/human CDR-grafted antibody comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or an antibody fragment comprising the VH chain of SEQ ID NO:55 and/or the VL chain of SEQ ID NO:56 or comprising VH CDR sequences of SEQ ID Nos:3-5 and/or VL CDR sequences of SEQ ID Nos:6-8 or wherein the antibody is conjugated to hIL-2. These deficiencies are made up for in the teachings of Shitara et al [c] and Queen et al and Nakamura et al.

Shitara et al [c] have been described supra.

Queen et al have been described supra.

Nakamura et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an anti-GD3 chimeric antibody (KM-871) comprising the KM-641 VH (residues 11-129 of SEQ ID NO:18) and VL (residues 21-127 of SEQ ID NO:19) chains and conjugate the chimeric antibody to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments thereof comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma

KM-641 (SEQ ID Nos:18 and 19) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced an anti-GD3 chimeric antibody (Km-871) comprising the KM-641 VH (residues 11-129 of SEQ ID NO:18) and VL (residues 21-127 of SEQ ID NO:19) chains and conjugate the chimeric antibody to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments thereof comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:18 and 19) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [c] and Queen et al and Nakamura et al because Shitara et al [c] teach chimeric antibody KM-871 (produced by transformant KM-871 (FERM BP-3512); see page 7, lines 46-50) that specifically reacts with GD3 expressed in human tumors and KM-871 comprises the constant region of human IgG1 linked to the variable region of the mouse monoclonal antibody KM-641, which is produced by hybridoma KM-641 (FERM BP-3116). Thus, KM-871 comprises the KM-641 VH (residues 11-129 of SEQ ID NO:18) and VL (residues 21-127 of SEQ ID NO:19) chains, and comprises VH CDRs of SEQ ID Nos:3-5 and VL CDRs of SEQ ID Nos:6-8 and Nakamura et al teach an I^{125} labeled antibody-hIL-2 immunoconjugate specifically enhances tumor vascular permeability whereas pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have

conjugated hIL-2 to chimeric antibody KM-871 (i.e., a polypeptide comprising residues 11-129 of SEQ ID NO:18 and is also a polypeptide comprising residues 21-127 of SEQ ID NO:19) taught by Shitara et al [c] to specifically increase tumor vascular permeability, thereby enhancing the therapeutic efficacy of chimeric antibody KM-871 in human tumors. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized anti-GD3 antibody and antibody fragments comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:3-8) and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:55 and 56) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [c] and Queen et al and Nakamura et al because Shitara et al [c] teach an anti-GD3 antibody (KM-871) comprising VH CDRs of SEQ ID Nos:3-5 and VL CDRs of SEQ ID Nos:6-8 and administered mouse monoclonal antibodies illicit an anti-mouse antibody response in human patients (see column 2, lines 18-23) and Queen et al teach humanized antibodies for human therapy, which are less immunogenic in human patients as compared to mouse antibodies (i.e., reduced HAMA response) and thus, overcome one of the limitations associated with administering mouse antibodies for human therapy and Nakamura et al teach an I^{125} labeled antibody-hIL-2 immunoconjugate specifically enhances tumor vascular permeability whereas pretreatment with IL-2 was not tumor specific. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have produced a

GD3 specific humanized antibody and antibody fragments thereof comprising the KM-641 VH CDRs of SEQ ID Nos:3-5 and/or VL CDRs of SEQ ID Nos:6-8 as taught by Shitara et al [c] and anti-GD3 antibody fragments comprising the VH and VL chains of SEQ ID Nos:55 and 56 (i.e., VH and VL chains of KM-641), respectively, and one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to conjugate hIL-2 to the anti-GD3 humanized antibody and antibody fragments thereof to specifically enhance tumor vascular permeability of the antibodies for increased therapeutic benefit of human tumors. Thus, it would have been obvious to one skilled in the art at the time the claimed invention was made to have produced an anti-GD3 chimeric antibody (Km-871) comprising the KM-641 VH (residues 11-129 of SEQ ID NO:18) and VL (residues 21-127 of SEQ ID NO:19) chains and conjugate the chimeric antibody to hIL-2 and to have produced a humanized anti-GD3 antibody and antibody fragments thereof comprising the CDRs from the VH and/or VL chain(s) produced by hybridoma KM-641 and antibody fragments comprising the VH and/or VL chain(s) produced by hybridoma KM-641 (SEQ ID Nos:18 and 19) and conjugate the humanized antibodies and antibody fragments to hIL-2 for therapeutic benefit of human tumors in view of Shitara et al [c] and Queen et al and Nakamura et al.

Claims 1-19, 24-29, 33-39, 48-54 and 63-66 are directed to an invention not patentably distinct from claims 1-2 of commonly assigned U.S. Patent 6,495,666 B2. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP

§ 2302). Commonly assigned U.S. Patent 6,495,666 B2, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Conclusion

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER